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Characteristics of biological therapy in pediatric patients with Crohn's disease

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Abstract:

Introduction: At present, there a is significant amount of data related to biologics used in pediatric patients with Crohn's disease. This review characterizes the different biological drugs administered in this population.

Areas covered: Biological therapy of CD, focusing on children, is summarized in this review. After mechanism of action and pharmacokinetics are described, mucosal healing on anti-TNF therapy, aspects of early therapy, long-term outcome and combination therapy are discussed. Moreover, loss of response and treatment optimization, as well as drug withdrawal are

summarized. Subsequently perianal disease and surgical aspects are discussed followed by safety issues. In addition, new drugs (vedolizumab, ustekinumab), cost effectiveness and administration of biosimilars were also included.

Expert commentary: There is significant data to characterize biological drugs administered in pediatric patients with Crohn's disease, however, head-to-head comparative studies using different biologics are missing.

Keywords: Crohn's disease, pediatric, biologics, infliximab, adalimumab, vedolizumab, ustekinumab, biosimilars, cost-benefit

1. Introduction

Crohn's disease (CD) is a chronic, relapsing, destructive, inflammatory disease with variable severity of gastrointestinal and extraintestinal involvement resulting in significant morbidity and impact on quality of life. Incidence of CD has been significantly increasing globally over the last few decades [1]. Pediatric-onset CD, accounting for one-quarter of all CD patients, is more extensive and severe at presentation with more aggressive disease course and worse prognosis when compared to adult-onset. The proportions of the 3 disease behaviors (inflammatory, stricturing, penetrating) are similar at presentation in childhood- and adult-onset CD with inflammatory phenotype being the highest proportion (approximately 75%) [2]. However, the rapid decrease of inflammatory phenotype in childhood-onset CD results in much shorter time ("window of opportunity") to use anti-inflammatory agents on the one hand and explains the increased need for surgery due to higher proportion of stricturing and penetrating phenotypes on the other hand. Currently there is no curative treatment for CD. Previously, management of CD was focused on controlling symptoms. Since the introduction of monoclonal antibodies against tumor necrosing factor alpha (TNF), one of the key cytokines in systemic inflammation, mucosal healing could also be achieved beyond controlling symptoms. With the use biologics the natural course of the disease can be altered by slowing down disease progression and extending the window of opportunity which in turns results in slower evolution of perforating or stricturing complications thus reducing intestinal surgery. In children, poor disease control not only affects nutrition but growth, puberty, bone health and psychosocial maturation also. Therefore, early aggressive treatment is recommended especially in childhood-onset CD.

2. Overview of the medical treatment of CD

Conventional medical therapy includes 5-aminosalicilates, corticosteroids and immunomodulators. Exclusive enteral nutrition is as good at least as corticosteroids when inducing remission in luminal disease, therefore it is recommended as first line therapy by current guidelines [3]. Failing conventional therapy requires escalating treatment to anti-TNF agents ("step-up" approach). However, there seems to be a rational in selected patients for first line use of potent anti-TNF agents with an aim to achieve mucosal healing and preventing perforating or stricturing complications and de-escalation of treatment to immunomodulators ("top-down" approach) later on. Anti-TNF agents on their own are more expensive than conventional medications, however, additional costs of hospital admissions for flare ups and treating complications, as well as disease related school absenteeism and impact on quality of life have to be also taken into consideration. When selecting the best possible treatment strategy, it would be useful if we could predict disease course and identify high-risk patients for flare-ups and complications. Current knowledge of indicators for complicated disease course in pediatric CD is summarized in Table 1.

The first biological agent approved for CD treatment was infliximab (IFX) in adults in 1998 and for children in 2006. IFX is a chimeric (75% human, 25% murine) monoclonal IgG_1 antibody against TNF. Subsequently adalimumab (ADA), fully human, monoclonal anti- TNF IgG_1 was also approved for CD treatment in adults in 2007 and in children in 2014.

IFX is given intravenously as an infusion at a standard dose of 5mg/kg at weeks 0, 2 and 6 as induction followed by 8 weekly infusions as maintenance therapy at the same dose. In case of loss of response (LOR) or low through levels, increasing the dose up to 10mg/kg and/or shortening the time between infusions to 6 or even 4 weeks should be considered.

ADA is administered as subcutaneous injection every 2 weeks with an initial dose of 2.4mg/kg (maximum 160mg) then 1.2mg/kg (maximum 80mg) as induction followed by 0.6mg/kg (maximum 40mg) as maintenance therapy. For practical considerations 160-80-

40mg regime can be given to patients over 40 kg and 80-40-20mg regime to those under 40 kg. In patients with LOR or low through levels weekly injections are indicated.

Less experience with vedolizumab (VDZ) and ustekinumab (UST) exist in the treatment of pediatric CD, however, case-series have been published already.

3. Pharmacokinetics and mechanism of action of infliximab, adalimumab, vedolizumab and ustekinumab

3.1. Structure

Monoclonal antibodies (mAb) are artificially synthesized immunoglobulin G (IgG) type therapeutic substances. IgG mAbs consist of two identical heavy chains and two identical light chains. Functionally, the mAbs have two types of domains: the variable region (Fab) is responsible for specific target antigen binding, and a constant region (Fc). IFX is a chimeric mAb composed of an engineered Fab region of murine origin and a human IgG1 Fc domain [4].VDZ, a humanized IgG_1 antibody, carries fewer murine derived regions compared to chimeric antibodies [5]. On the other hand, ADA and UST are a fully human recombinant IgG_1 molecules composed of recombinant human-derived Fab regions specifically binding to the target protein and a human IgG_1 Fc [6, 7].

3.2.Mechanisms of Action (molecular biologic)

IFX and ADA exert their main biological effect via binding to soluble and transmembrane forms of TNF with high affinity, and neutralizing its function. TNF is a major pro-inflammatory cytokine witch activates NF-κb, MAPK, and caspase signaling pathways on various cell types. IFX and ADA bind with near equal affinity to TNF and neutralize TNF dependent downstream signaling effects, therefore the different clinical efficacy profiles of

these drugs are not explained by intrinsic binding property differences [8]. Besides the disruption of downstream inflammatory signaling originating from the receptor binding of soluble TNF, both drugs are capable to elicit complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity via the functional Fc region of the antibodies which bind to the transmembrane form of TNF. One of the effect elicited in an Fc dependent manner is the induction of regulatory macrophages resembling the anti-inflammatory M2 macrophage phenotype. These macrophages can inhibit ongoing immune response and promote tissue repair and ~~the~~ resolution of inflammation. The induction and function of these effector cells are autophagy dependent, therefore it requires an intact autophagy pathway, however the presence of certain risk alleles can reduce the patient's ability to generate these macrophages [9]. Given the complex and pleiotropic downstream effects of TNF signalization, the full extent of mechanisms culminating in alleviation of inflammation is still a matter of active research.

VDZ is a humanized mAb that selectively binds to the α4β7 integrin and blocks α4β7 integirin-MAdCAM-1 interaction. This integrin-adressin interaction is specific to the intestinal tissues and plays a central role in gut-homing of T-cells, therefore VDZ is able to elicit gut-selective anti-inflammatory effects [5]. By neutralizing α4β7 integrin VDZ prevents initial binding, rolling and subsequent flattening and transendothelial migration of T-cells to the intestinal wall, thereby specifically inhibits gut-homing of lymphocytes, which phenomenon is one of the key factors of the pathomechanism of inflammatory bowel disease (IBD) [10].

UST is a fully human monoclonal antibody that specifically binds to p40, a shared protein subunit of the heterodimeric cytokines IL-12 and IL-23. UST, by preventing the receptor binding, has an inhibitory effect on several inflammatory and immune functions. UST is unable to bind to already formed cytokine-receptor complexes on the cell surface, therefore it

is unlikely to elicit Fc effector functions such as complement- and antibody-mediated cytotoxicity in cells expressing IL-12 and IL-23 receptors [6, 11].

3.3.1.Absorption and distribution

The different route of administration of mAbs determine the basic pharmacokinetic properties of these therapeutic agents. IFX and VDZ is administered intravenously (i.v.), therefore it reaches high peak concentration and high bioavailability (approximately 100%) shortly after infusion. The i.v. route of administration of mAbs is usually linked with less variability of exposure between patients, and decreased risk of immunogenicity [7]. ADA (less immunogenic, 100% human) is administered subcutaneously (s.c.) and absorbed mainly by lymphatic drainage. This route of absorption is significantly slower with maximum concentrations of mAbs achieved 8-10 days after administration and could result in bioavailability ranging between 50-100% depending of the dose absorbed by patients [4]. In addition, s.c. administration has a higher potential for immunogenicity due to the highly specialized foreign antigen processing of the skin and the lymphatic system. UST can be administered i.v. or s.c. as a weight-based infusion or as a fix-dose injection [12].

3.3.2.Elimination and clearance

Renal elimination does not play a significant role in mAb clearance. mAbs are not directly excreted in urine, they are degraded to peptides or amino acids. These components could be reused in anabolic metabolism, or ~~got~~ excreted by the kidneys [4]. mAbs eliminated from the

body by proteolytic mechanisms, mainly by the reticuloendothelial system in an Fc gamma receptor mediated endocytosis. After binding to the receptor, mAbs are internalized and degraded. Counteracting this mechanism, antibody binding to the Brambell RcRn-receptor activates a salvage pathway that prolongs the serum half-life of IgG antibodies by recirculation of the antibodies after endocytosis [13]. Due to this recirculatory pathway IgG antibodies have a prolonged half-life (2-3 weeks) compared to other immunoglobulin isotypes (2-3 days) [4]. Accordingly, the approximate half-life of IFX and ADA is two weeks, of VDZ and UST is three weeks [14, 15].

3.3.3.Factors affecting elimination

Due to the inherent immunogenicity of protein macromolecule therapeutics and the need of continued dosing for efficacy there is risk that patients develop anti-drug antibodies over the course of the therapeutic regimen.Anti-drug antibody (ADab) formation is associated with increased clearance caused by immune complex formation between the therapeutic agent and ADab-s, and neutralization of the therapeutic antibodies. ADab-s significantly alter bioavailability and serum half-life of mAb therapeutic agents by facilitating clearance [7].

If the ADab is neutralizing, it could directly alter the effectiveness of the drug. Non-neutralizing antibodies does not necessarily affect the mechanism of action, but the mAb-ADab complexes are not recirculated after internalization via the Brambell receptor pathway, instead they are retained and proteolized [7].

IFX pharmacokinetics could be significantly affected by patient factors, most importantly body weight, albumin levels and the presence of ADab [16]. The main factors reported to affect-pharmacokinetic properties of ADab are previous exposure of biologicals, body weight, CRP-level, albumin-level, ADab formation, and concomitant immunomodulator use and

disease activity [17]. In clinical trials investigating the pharmacokinetics of VDZ, body weight, ADab levels, disease activity, albumin levels were reported as clinically relevant predictors of clearance and drug levels [15]. In case of UST, the main factors affecting drug clearance were body weight, presence of diabetes mellitus and ADab formation [18].

4.Anti-TNF treatment in CD

4.1.Main clinical trials with infliximab and adalimumab

Biological therapy has revolutionized treatment of CD with several landmark studies demonstrating IFX and ADA as safe and effective agents for inducing and maintaining remission. Historically these studies were initially done in adults followed by pediatric trials. The ACCENT I study demonstrated that IFX can induce remission and regular 8 weekly infusions were more effective in maintaining remission when compared to episodic treatment in adult CD patients with luminal disease [19]. Furthermore, dose escalation to 10mg/kg was found to be effective in regaining clinical response in patients who lost response on 8 weekly 5mg/kg IFX infusions [20].

In the REACH study safety and efficacy of IFX as induction and maintenance therapy of moderate to severe CD, despite prior corticosteroid and immunomodulator therapy, was evaluated in children aged 6-17 years [21]. IFX at a dose of 5mg/kg was given to 122 children with active CD at weeks 0, 2 and 6 ("standard induction regime"). Out of 122 children, 88% responded to treatment and 59% entered remission at week 10. Subsequently week 10 responders were randomized to either 8 weekly or 12 weekly 5mg/kg IFX as maintenance therapy with continuation of immunomodulator therapy. At week 54, clinical remission rate without the need for dose escalation in the 8-weekly interval group was 56% compared to 24% in the 12-weekly scheduled group.

The CLASSIC-I and CLASSIC –II trials demonstrated higher remission rates in induction and in maintenance treatment with higher ADA doses in anti TNF-naïve adult patients with moderately to severe CD [22, 23].

In the IMAgINE 1 trial safety and efficacy of ADA was evaluated in 192 children aged 6-17 years with moderate to severe CD despite prior corticosteroid and/or immunomodulator

therapy [24]. Patients with previous IFX treatment who showed initial response but IFX was subsequently discontinued due to LOR or intolerance were also eligible to participate. This study was the first double-blind randomized trial of ADA in children. An open-label induction with ADA at weeks 0 and 2 (160mg and 80mg over 40kg, and 80mg and 40mg under 40kg) was followed by randomization at week 4 to high or low dose ADA double blind maintenance therapy for 48 weeks. ADA was given every other week at a dose of 40mg over 40kg and 20mg below 40kg in the high dose group, whereas in the low dose group 20mg ADA was given over 40kg and 10mg below 40kg. Clinical remission rate was 33.3% in the high dose group compared to 23% in the low dose group at week 52 (P=0.1). In the high dose group IFX naïve patients had a much higher remission rate at week 52 when compared to those who received IFX previously but was discontinued due to LOR or intolerance (45% vs 19%, respectively).

ADA was found to be effective as both first line treatment of CD and as second line therapy in case of primary non-response to IFX or failure of IFX therapy due to LOR or IFX intolerance.

Efficacy of ADA treatment in 53 children with CD who failed IFX therapy was evaluated in a retrospective nationwide observational study with a median follow-up of 1 year [25]. Reasons for discontinuing IFX therapy were as follows: LOR (64%), allergic reaction (21%), adverse effect (9%) and primary non-response (6%). The median duration of treatment with IFX was 15.5 months. Sixty-four percent of patients achieved remission whereas 34% failed ADA treatment (7.5% non-response, 21% LOR and 5.5% adverse effect). Remission was achieved after a median of 3.3 months and 50% of those who achieved remission still maintained this after 2 years. Two third (12/18) of failures with ADA treatment occurred by 12 months of

follow-up. Only 1 out of 3 patients with primary non-response to IFX could achieve remission with ADA and 24 of 34 patients achieved remission with ADA after LOR to IFX.

4.2.Mucosal healing

Since anti-TNF agents demonstrated that mucosal healing can be achieved, deep remission (clinical remission with mucosal healing) has been proposed as the desired target when treating CD.

Complete mucosal healing and clinical remission rates at week 10 were 23% and 33%, respectively after 3 doses of standard IFX induction regime in 66 children with moderately to severe CD naïve to anti-TNF agents [26].

Primary non-response rate was 28%. Mean age at diagnosis and initiation of IFX was 8.4 years and 14 years, respectively.

In a recently published retrospective single-center study 17% of 23 children with moderately to severe CD achieved complete mucosal healing and 65% showed endoscopic response on ADA induction therapy [27]. Mean age at diagnosis and at initiation of ADA treatment were 5.5 years and 13 years, respectively and almost one third of children had previous IFX therapy. Significant decrease was found in SES-CD on post-induction endoscopy when compared to baseline.

Complete, partial and no mucosal healing rates at follow-up endoscopy were 38%, 32% and 30%, respectively in a prospective study in 37 children with CD naive to biologic therapy with a mean disease duration of 13 months at enrolment [28]. No significant difference in complete or partial mucosal healing rate was found when IFX or ADA was used. In addition, no statistical difference was found in rates of mucosal healing when initiating anti-TNF treatment earlier than 1 year or after 1 year of disease duration. Clinical remission rates on

anti-TNF maintenance therapy 1 and 2 years after follow-up endoscopy were 70.3% and 59.5%, respectively. However, clinical remission rates of those who achieved complete mucosal healing on follow-up endoscopy were 100% and 79% after 1 and 2 years of follow-up endoscopy, respectively. Complete mucosal healing was similar with anti-TNF monotherapy or with combination of anti-TNF therapy with either azathioprine (AZA) or methotrexate.

In a retrospective single center study in 33 children with CD receiving anti-TNF therapy, mucosal healing rate after 12 months of IFX and ADA treatment was 22% and 25%, respectively and clinical response rate was 84% and 92%, respectively [29].

4.3.Early therapy

Anti-TNF agents have demonstrated their ability to change the natural course of the disease therefore early use or even starting anti-TNF after diagnosis (top-down therapy) might offer benefits when compared to conventional step-up approach. This is a particularly important aspect in children in whom the window of opportunity is considered shorter than in adults and in whom uncontrolled disease has a negative impact on linear growth and maturation, as well. However, not all patients might need immediate anti-TNF therapy after diagnosis, therefore careful selection of those patients who would benefit from early anti-TNF therapy is essential to avoid over-treating others.

Anti-TNF monotherapy (IFX or ADA), immunomodulator monotherapy or no immunotherapy introduced early in treatment (within 3 months from diagnosis) compared in an observational study using propensity score matching in 552 newly diagnosed children with inflammatory phenotype CD [30]. Percentages of patients receiving additional treatment between 3 and 12 months after diagnosis were as follows: 10% of anti-TNF monotherapy patients received immunomodulator, 29% of immunomodulator only patients had subsequent

anti-TNF therapy and 69% on no early immunotherapy patients received anti-TNF and/or immunomodulator therapy. Remission rates at 1 year in the early anti-TNF, early immunomodulator or no immunotherapy groups were 85.3%, 60.3% and 54.4%, respectively. Remission rate at 1 year with later introduction (between 3 and 12 months after diagnosis) of anti-TNF in the early immunomodulator group was 58%. It was the early anti-TNF group only in which significant increase in height z-score was observed within this 1 year. This study demonstrated the advantage of early anti-TNF use in pediatric CD and the need for early aggressive treatment.

The effect of early (within 1 month of diagnosis) combined immunosuppression with IFX+AZA without corticosteroid (CS) induction on mucosal healing in children with moderately to severe luminal CD was compared to conventional step-up treatment initiated by 8 weeks of CS induction in a prospective observational study by Kang *et al* [31]. In the conventional step-up group (28 patients, mean age at diagnosis: 14.2 years) CS, AZA and mesalazine were started after diagnosis and treatment was escalated to IFX in case of steroid refractory or steroid dependent induction or relapse after successful induction with CS without changing AZA and mesalazine therapy. Median time from diagnosis to initiation of IFX was 8.1 months in this group. In the early combined immunosuppression group (48 patients, mean age at diagnosis: 15 years) IFX, AZA and mesalazine were started after diagnosis. IFX was given in standard doses as described earlier and dose intensification was allowed in both groups in case of relapse or LOR. Mucosal healing rate at week 14 and 54 after initiation of IFX in the early IFX group was significantly higher when compared to conventional step-up group; 51% vs 32%, and 74% vs 42%, respectively. Neither baseline SES-CD nor deep ulcers on ileocolonoscopy were predictors for mucosal healing at week 14 or 54. This study showed a lower rate of mucosal healing with later introduction of IFX indicating a short window of opportunity in children due to the progressive nature of the

disease and clearly demonstrated the advantage of early aggressive treatment with concomitant IFX +AZA therapy over conventional step-up approach.

In a recently published multicenter, prospective inception cohort study using propensity score matching, the effect of early anti-TNF therapy (within 90 days of diagnosis) on stricturing or penetrating complication risk was evaluated in 913 children with newly diagnosed CD [32]. The risk for penetrating complication with early anti-TNF treatment was 1/3 when compared to those without early anti-TNF therapy, however stricturing complication was similar irrespective of early anti-TNF therapy.

4.4.Long term outcome of anti-TNF treatment

Maintaining remission after successful induction is the key element of long-term treatment. Unfortunately, the effect of biological agents wears off with time, however it has been shown previously that optimization of therapy can help regaining clinical response in those who lost response.

Long-term outcome with anti-TNF therapy (IFX and ADA) was evaluated in 102 children with CD in a multicenter retrospective study [33]. Median disease duration and mean age at initiation of anti-TNF therapy were 15 months and 11.3 years, respectively and median duration of anti-TNF therapy was 15 months. IFX (82% of patients) and ADA (18% of patients) were given in standard doses as described earlier. Primary response rate to induction was 89%, whereas the rate of losing response was 18%, 35% and 46% at 1, 3 and 5 years, respectively. Eleven percent of primary responders required temporary treatment intensification (either dose escalation or interval shortening) during maintenance therapy with good clinical response allowing to return to standard treatment schedule later on. No predictors for LOR could be identified in this study.

Remission rates at 12, 24 and 36 months were 60.9%, 79% and 87.5%, respectively with 35% of patients requiring dose optimization in an Italian retrospective observational study of 78 children on long term anti-TNF therapy (61.5% IFX and 31.5% ADA) for CD [34]. The cumulative probability of discontinuing anti-TNF therapy at 1, 2 and 3 years after initiation was 19%, 56% and 67%, respectively. Mean age and disease duration at initiation of therapy was 15 years and 40.6 months, respectively. Thirty-six percent of the patients had shorter disease duration than 1 year. In this study, disease remission was the major cause for treatment discontinuation, however, 50% of these patients relapsed at a mean time of 12.8 months.

Similarly, a Dutch multicenter observational study in 152 children treated with IFX for CD demonstrated 13%, 40% and 50% of cumulative probability of losing response after 1, 3 and 5 years, respectively [35]. In 502 children with CD on long-term IFX therapy participating in a prospective multicenter study 84%, 69% and 60% still remained on IFX therapy after 1, 3 and 5 years, respectively [36].

In a recently published Canadian retrospective, multicenter study long-term outcomes with IFX therapy was evaluated in 180 children with CD [37]. IFX was started at a median disease duration of 1.5 years and at a mean age of 14.3 years with a median follow-up of 85.9 weeks. Percentage of children still on IFX therapy at 1 and 2-year follow-up was 95.5% and 91%, respectively. Treatment intensification with increasing dose and/or shortening intervals occurred in 57.3% of patients, whereas discontinuation of IFX treatment due to LOR was 3.2% of patients per year.

In the IMAgINE 2 study (open label extension of IMAgINE 1) response and remission rates at year 5 on ADA maintenance treatment were 48% and 41%, respectively [38]. Forty-five percent of patients maintained remission from enrollment to IMAgINE 2 until finishing the study.

No significant difference in effectiveness and safety of 315 ADA-treated and 512 IFX-treated biologic-naïve adult CD patients over a 2.3 years median follow-up was found in a Danish population-based, propensity score matched, real-life cohort study published in 2017 [39]. Similar levels of persistence as first- and second-line anti-TNF treatments were demonstrated with IFX and ADA in a 14-year single-center experience with adult CD patients [40].

4.5.Combination therapy

The advantage of combination therapy with an anti-TNF agent and an immunomodulator have been investigated in several studies. The SONIC study was the first landmark trial demonstrating better outcomes with combination therapy in adults with moderately to severe CD naïve to both immunomodulators and anti-TNF therapy. Patients randomly received 2.5mg azathioprine (AZA) only, or scheduled 5mg/kg IFX infusions only or the combination of these drugs. Corticosteroid-free remission rates at week 26 and at week 50 in combination group, IFX only group and AZA only group were 56.8%, 44.4% and 30%, and 46.2%, 34.9% and 24.1%, respectively. Mucosal healing at week 26 was 43.9%, 30.1% and 16.5%, respectively [41].

The COMMIT trial compared combination of IFX with methotrexate (MTX) and IFX only maintenance therapy after corticosteroid induction in adult CD patients [42]. IFX was given at standard induction and maintenance doses, whereas the initial dose of MTX was 10mg/week followed by escalation to 20mg/week and later to 25mg/week. Corticosteroid-free remission rates by week 50 in IFX+MTX combination group and in IFX only patients were 56% and 57%, respectively. However, antibody formation against IFX was much lower and IFX trough levels were higher in the combination group when compared to IFX only patients (4% vs 20% and 6.35 μg/ml vs 3.75 μg/ml, respectively) demonstrating that MTX could prevent antibody formation against IFX.

In children the long term durability of IFX treatment in 502 anti-TNF naïve CD patients with concomitant immunomodulator use was evaluated in a multicenter prospective study [36]. Mean age at diagnosis and at IFX initiation was 11.8 and 13.2 years, respectively. Proportion of children remaining on IFX therapy after 1, 3 and 5 years were 84%, 69% and 60%, respectively. Longer (over 6 months) concomitant immunomodulator therapy was associated with higher probability of remaining on IFX therapy for 5 years when compared to short (less than 6 months) or no concomitant immunomodulator use (70%, 55% and 48%, respectively). When concomitant AZA and MTX therapy over 6 months was compared in boys, probability of IFX treatment for 5 years was 97% with MTX and 58% with AZA.

In a single-center retrospective analysis of 195 children with luminal CD on long-term IFX therapy, LOR was significantly lower in patients with more than 30 weeks of concomitant immunomodulator (AZA or MTX) use when compared to IFX monotherapy (hazard ratio: 0.25) [43]. Median age at diagnosis was 13.9 years and median time from diagnosis to initiation of IFX was 1.6 years. Male gender and early IFX use were associated with complete response. Rate of LOR was 2-6% per year over 5 years.

In the study of Kang *et al.* mentioned earlier, significantly higher mucosal healing rate was found after 1 year of treatment in children with early combination therapy with IFX+AZA when compared to conventional step-up therapy (74% vs 42%, respectively) [31].

Addition of thiopurine (n=14) or MTX (n=9) to ADA as salvage combination therapy was evaluated in 23 patients with IBD (21 CD and 2 ulcerative colitis) who lost response on ADA monotherapy due to antibody formation [44]. Combination therapy was successful in regaining response by elimination of antibodies and by increasing trough levels in 48% of patients. Response was not affected by baseline clinical characteristics or the type of immunomodulator added to ADA.

In a recent study published by Strik *et al.* 77% success rate was achieved in restoring clinical response by clearance of anti-drug antibodies and increasing trough levels with salvage combination therapy of MTX or thiopurine to anti-TNF monotherapy in IBD patients who lost response due to immunogenicity [45].

These findings are very important when trying to maximize the use of a particular anti-TNF agent before switching to another biological agent. Salvage combination therapy with immunomodulators have been shown to be effective in restoring clinical response by eliminating anti-drug antibodies and increasing serum drug concentration, however concomitant use of immunomodulators might prevent or delay LOR.

Although advantage of combination therapy in terms of efficacy has been demonstrated in several studies, time of initiation and the length of concomitant immunomodulator therapy, as well as the choice of thiopurine or MTX are questions still awaiting to be answered.

4.6.Loss of response, optimization of treatment, regaining response

Patients not responding to induction with anti-TNF are considered primary non-responders. Percentage of these patients varies from 13 to 40 % in clinical studies [46].

After a successful primary response to induction therapy with anti-TNF, losing response might be best described as worsening of symptoms due to inflammatory activity of IBD on anti-TNF treatment requiring modification of treatment. Non-inflammatory mechanisms (e.g. Functional abdominal pain/Rome IV, fibrostenotic stricture) or inflammatory mechanisms not related to IBD: infection (e.g. *Clostridium difficile*, CMV) and celiac disease can also cause worsening of symptoms on anti-TNF treatment and therefore have to be carefully evaluated before intensification of immunosuppression.

However, different definitions for LOR (e.g. dose escalation or anti-TNF discontinuation) used in clinic trials accounts for difficulties when comparing rates of LOR to various anti-TNF agents.

LOR over time is not linear but with a steeper decrease within the first year and a much slower rate in the following years. When LOR was defined as the need for treatment escalation in landmark studies, the cumulative rate of LOR to anti-TNF within 1 year ranged from 23% to 46% for both IFX and ADA [47]. LOR based on drug discontinuation rate (despite anti-TNF therapy intensification) is 5-13%.

One of the causes of LOR is low trough levels of anti-TNF agents. Antibody formation against an anti-TNF agent and increased drug clearance can also result in lower serum levels of the drug. Therefore, monitoring antibody levels with simultaneous drug levels are the cornerstone of individually optimized treatment. In reactive monitoring therapeutic drug monitoring (TDM) is used in LOR. Low drug level with low level/absence of antibodies suggest undertreatment (pharmacokinetic failure) in LOR and therefore necessitates treatment intensification by increasing the dose and/or shortening the interval between two doses. In landmark studies the rate of regaining response to IFX and ADA with intensification of treatment ranged from 60% to 80% [47]. However, low anti-TNF level with simultaneously high antibody titers in LOR indicate neutralization of that particular anti-TNF agent (immunogenic failure) and switching to another drug within the same class or to a different drug class (non-anti-TNF) have to be considered. Recent studies demonstrated that addition of an immunomodulator was successful in regaining clinical response by eliminating antibodies [44, 45]. LOR with adequate drug level with low level/absence of antibodies suggest refractory disease to anti-TNF (pharmacodynamic failure) and therefore switching to out-of-class agent should be considered.

In the TAXIT trial (Trough Concentration Adapted Infliximab Treatment) with adult IBD patients IFX was initially optimized to reach a target trough level of 3-7 μg/ml followed by randomization to receive either clinically based or through level-based (proactive monitoring) maintenance IFX dosing for 1 year [48]. Remission rates at 1 year were similar in clinically and drug level based treatment (66% and 69%, respectively), however relapse rate during maintenance therapy was significantly lower with trough level-based therapy when compared to clinically based dosing (7% vs 17%).

Therapeutic drug monitoring (TDM) is not only cost-effective but has a potential safety benefit by reducing supra-therapeutic drug levels. TDM at pre-specified time points (proactive monitoring) offers further benefit in optimized treatment when compared to reactive monitoring.

In a Dutch retrospective observational study with children suffering from CD with a median disease duration of 12 months when IFX was initiated, 15% of 162 patients developed antibodies to IFX (ATI) at a median of 14 months after IFX therapy was commenced [49]. Proportion of children developing ATI in IFX monotherapy and combined immunosuppression (IFX+thiopurine or MTX) groups were 42% and 11.8%, respectively. LOR to IFX was 64% among patients with ATI and 19% in those without ATI.

LOR to IFX was evaluated in a Canadian single center retrospective study in 248 children with CD [50]. Median duration of disease was 0.9 years and median age was 14.8 years at initiation of IFX. Primary non-response rate was 21% and 79% of children responded (57% clinical remission and 22% clinical response) to induction. LOR in the latter group (196 children) was 16% after a mean of 1.6 years of treatment, whereas 64% of primary responders were still on IFX therapy after a mean of 2.2 years. The rate of IFX optimization and requirement for additional treatment during IFX maintenance therapy in primary responders were 33% and 48%, respectively. Steroid resistance in induction was the only independent

predictor for primary non-response, and partial responders to induction (clinical response only but not achieving clinical remission) and isolated colonic disease were predictors for LOR.

In a recently published Belgian retrospective study in 52 pediatric patients with IBD (33 CD and 19 UC) serial proactive TDM and dose adjustment to aim for 3-7 µg/ml trough IFX level during maintenance therapy resulted in higher endoscopic and clinical remission rates associated with higher IFX trough levels arguing the need for proactive TDM in children in order to improve long-term outcomes [51].

4.7.Drug withdrawal

When conventional therapy fails and biologic therapy is introduced as escalation of treatment it seems reasonable to consider stopping immunomodulators to decrease the risk of side effects and to continue with biologic therapy only (i.e. monotherapy). However, continuation of combination therapy might offer benefits as well (e.g. preventing antibody formation against anti-TNF). After a prolonged time in remission on combination therapy, stopping either anti-TNF or immunomodulator due to safety concerns and cost-effectiveness seems reasonable, however from efficacy point of view might be disadvantageous.

The STORI trial demonstrated that, after more than 6 months of CS-free remission in 115 adult CD patients on at least 1 year of combination therapy, stopping IFX and continuing with immunomodulator resulted in 43.9% relapse rate within 1 year [52].

When immunomodulator therapy was discontinued and maintenance IFX monotherapy was given in a randomized trial on adult CD patients in remission for at least 6 months on combination therapy, similar rates of IFX failure was observed in IFX monotherapy patients when compared to those who continued combination therapy [53]. However lower IFX trough levels and higher CRP values were associated with discontinuation of immunomodulators.

Relapse rates and time to relapse after 1 year of successful IFX treatment were evaluated in two Hungarian observational studies. Patients were in clinical remission when IFX was stopped at the end of 1-year treatment and were followed-up for a further 1 year.

In the PIT-STOP (Pediatric IFX Treatment Stop) study, 99 children with CD were enrolled [54]. Median age at diagnosis and disease duration when IFX was initiated were 13.1 years and 1.7 years, respectively. More than half of the patients (55%) required reintroduction of IFX after a median follow-up of 0.8 years. Risk factor for restarting anti-TNF therapy was steroid use at the time of initiating IFX therapy.

These results were similar to the RASH study (Relapse After Stopping biologicals in Hungary) in adults with CD who achieved clinical remission on 1 year anti-TNF therapy (87 patients on IFX and 34 on ADA) [55]. Anti-TNF therapy was restarted in 45% of 121 patients at a median time of 6 months. Predictors for restarting anti-TNF therapy were previous biological therapy and treatment intensification during 1-year anti-TNF therapy.

4.8.Surgery

Childhood-onset CD has a much worse phenotype and prognosis requiring earlier surgical interventions when compared to adult-onset CD with a risk of 48% vs 5% of extensive intestinal resection at the age of 30 years [56]. Modifying the natural course of the disease with the use of anti-TNF agents might delay intestinal resection. However, because of the rapid rise in incidence of IBD, the total number of surgical procedures in pediatric CD have been increasing.

In a register-based observational cohort study published in 2017, risk of first bowel resection was evaluated in Swedish patients (children and adults) with no previous bowel resection for

CD [57]. At the time of diagnosis 22% were younger than 17 years, and 19% were older than 40 years. Median disease duration at anti-TNF initiation was almost 8 years and 65% of 1856 patients were still receiving anti-TNF therapy after 1 year. The cumulative rates for surgery within 1-7 year of anti-TNF therapy were 7%, 13%, 17%, 20%, 23%, 25% and 28%, respectively. No difference was found in bowel resection rates when anti-TNF therapy was discontinued within 1 year or given beyond 1 year and no predictors were found for bowel resection.

Anti-TNF therapy was evaluated after intestinal resection in anti-TNF naïve pediatric CD patients and in those with failure of pre-operative anti-TNF therapy despite adequate trough levels [58]. Re-treating patients with the same agent, after resection of anti-TNF refractory inflamed intestinal segment, was successful despite previous pharmacodynamic failure. Clinical remission rates in anti-TNF naïve and in re-treated patients after 1 year of post-operative anti-TNF therapy and at the end of follow-up (1.8 years) were similar (88.5% vs 89% and 80% vs 83%, respectively).

ECCO/ESPGHAN guideline recommend postoperative maintenance treatment with thiopurines as first choice drug and supplementary enteral nutrition or anti-TNF agents as possible option in selected cases [3]. Two meta-analyses demonstrated that in adult CD anti-TNF monotherapy appeared to be the most effective clinical and endoscopic postoperative prophylaxis [27, 59]. NASPGHAN Clinical Report suggest prophylactic intervention in pediatric patients with moderate to high risk of recurrent disease based on adult data and a recent Dutch multicenter cohort analysis when none of the patients on immediate postoperative anti-TNF treatment had surgical recurrence [60, 61].

4.9.Perianal disease

Incidence of perianal disease - an aggressive and disabling phenotype - in pediatric CD varies from 10% to 62%. Careful assessment of the extent and complexity of perianal disease is a typical multidisciplinary task requiring surgical, endoscopic and radiologic evaluations.

The ACCENT II was a landmark study which showed that in adult patients with fistulizing (abdominal or perianal) CD maintaining remission after 3 loading doses of IFX was more effective with 8 weekly scheduled maintenance IFX therapy than placebo (36% vs 19%) [62]. Complete closure of draining fistulas (enterocutaneous or perianal) at week 26 and 52 on ADA treatment in the CHARM trial was 30% and 33%, respectively [63].

Response rates in children with concurrent perianal CD who received IFX in the REACH study at week 2, 6, 10, 30 and 54 were 41%, 73%, 73%, 68% and 73 %, respectively and complete healing occurred in 23%, 59%, 64%, 59% and 68%, respectively [64]. In a French study of 101 children with perianal CD, primary response to IFX was 88% (52% complete healing), response and complete healing rate at 1 year was 75% and 53%, respectively [65]. Predictors for relapse in primary responders were more than one fistula and shorter duration than 10 months with CD. The rate of perianal findings and fistulizing perianal CD in 234 children from the ImageKids database were 24% and 9%, respectively [66]. Predisposition to greater inflammatory burden, association with distinct phenotype and more rectal and jejunal involvement were found in pediatric perianal CD.

Recent guidelines from the Pediatric IBD Porto Group of ESPGHAN suggest incision and drainage of abscesses, placement of non-cutting setons in symptomatic fistulae followed by anti-TNF therapy for at least 1 year in case of abscess drainage [67]. In a retrospective study no significant difference was found in clinical efficacy when comparing of IFX and ADA in the treatment of 47 adult CD patients with perianal fistulas [68].

4.10. Side effects and complications

TNF inhibitors are considered to be the most effective drugs for treatment of chronic inflammatory disorders reshaping their disease course. Their widespread use is associated with a high-rate of immune-mediated and nonimmune-mediated adverse reactions. Their toxicity may sometimes be related to the concomitant therapy or combination of other immunomodulatory agents leading to opportunistic infections or malignancies such as lymphomas. Furthermore, IBD itself may be associated with complications, such as arthralgia or arthritis, pustular skin eruptions, intestinal stricture, which may be related to anti-TNF therapy, as well [69]. Clinical trials and studies focus on adult patients not always making difference between CD and UC leading to the lack of systematic data in the pediatric population.

4.10.1. Skin

Skin is the most frequently involved organ affected by anti-TNF adverse reactions in IBD patients (highest incidence: 30.8% in the Nancy Cohort) [70]. Among adult patients, mainly bacterial and fungal skin infections and psoriasiform lesions are frequently observed. The incidence of anti-TNF-induced lupus-like syndrome, cancer and other skin reactions is usually <1%. Fréling and al found that younger age (<28 years) at drug initiation and CD were associated with increased risk of dermatological complications. The prolonged use of immunosuppressive agents was linked to increased risk of skin infections [70].

The main predictive factors for developing psoriasis are female gender and smoking. In the study of Andrade et al, ADA influenced the risk of anti-TNF-induced psoriasis [71]. In contrast, Mälkönen et al observed skin reactions in 47.6% of children in a 2-year prospective

study. Younger age, longer duration of treatment, higher number of infusions and the presence of CD showed significant association with skin lesions. Mainly the face, ears and flexural areas were involved by psoriatic reactions. Surprisingly, most patients were inactive or mildly active when the skin reaction appeared. The authors concluded that various methodological issues led to the pronounced differences in the prevalence of skin involvement [72].

4.10.2. Nervous system

Most of the reported IBD-associated neurological complications are connected to immune reactions, or may be consequences of thromboembolic events, nutrient deficiency and medication. The reported incidence of neurologic complications varies between 0.2-47.5% in IBD patients.

TNF blockers predispose for central or peripheral demyelination, vasculitis-induced nerve ischemia, or inhibition of direct signaling support for axons [73]. Rare, but dreadful complications include demyelinating disorders including multiple sclerosis, demyelination polyneuropathy and optic neuritis. In the pre-biologic era their prevalence was two-fold in CD compared to matched controls (OR 2.1; CI 0.9–4.5) [74]. The overall incidence of peripheral neuropathy and central demyelination in autoimmune diseases was 0.2 and 1 per 1000 patient-years for IFX and ADA, respectively [75]. In a large Spanish registry (BIOGEAS project), 175 central demyelinating cases and 44 cases of peripheral demyelination polyneuropathy were reported [76].

Regarding rare complications, cranial nerve palsy, myopathy, myelopathy, cerebral vasculitis, autonomic dysfunction may occur in less than 2% of adult IBD patients. Progressive multifocal leukoencephalopathy was identified only in 3 cases worldwide, specifically

connected to natalizumab treatment. There are neither systematic reviews, meta-analyses nor retrospective studies in anti-TNF treated pediatric IBD patients focusing on neurological complications.

4.10.3. Infection

Upper respiratory and urinary tract infections are the most common infectious manifestations in patients treated with anti-TNF agents. The incidence of opportunistic infections (nocardiosis, hystoplasmosis, herpes zoster, candidiasis, etc.) varies between 0.3-0.9% in different adult groups, but most patients received other immunosuppressive co-medications [69]. The meta-analysis of Ford et al reported significant difference in infections between anti-TNF- and placebo-treated IBD patients (RR 2.05; 95% CI 1.10-3.85). Treatment with other immunosuppressants or duration of anti-TNF treatment had no significant impact on the frequency of infections [77]. Another meta-analysis of placebo-controlled trials found no increased risk of overall infections in CD patients receiving anti-TNF therapy [78]. Mycobacterial infections were generally observed in patients with prior exposure to tuberculosis (TB) [69]. In the analysis of Ford et al, the relative risk (RR) for developing TB was not higher on anti-TNF therapy than on placebo (RR 2.52; 95% CI 0.62-10.21) [77]. In a single-center retrospective pediatric study, TB incidence was 6.4 per 10.000 person years (95% CI 0.9-45.4) in an anti-TNF-treated rheumatoid arthritis (RA) and IBD population. One report demonstrated a case of a 13-year-old girl with CD associated with disseminated TB infection after 34 months ~~long~~ treatment. In the region of the reported case (Alabama, USA) the TB incidence of 0-19 year-old healthy children was 0.064/10.000 [79]. Interferon-γ release assay seems to be an adequate screening test before the introduction of anti-TNF treatment. A multinational study from the Porto Pediatric IBD group registered 14 deaths from infection (14 cases from 31 (45%)) during a six years long period (2006-2011),

retrospectively. Infectious-related mortality cases included sepsis, candida and varicella infections. No tuberculosis, neither Pnarmocystis jimvecy infection were verified. Three patients (all of these patients had CD) were fed parenterally via central venous access. Eight patients were on combination therapy of immunomodulators containing biologics, too [80]. In a prospective multicenter study, the Porto Pediatric IBD group registered five infection related mortality from 26 cases (3 CD, 1 IBDU, 1 UC) between 2013-2016. Cause of death was sepsis in four cases (unknown infectious agent, one on total parenteral nutrition via central line catheter) and disseminated tuberculosis in one case. Just two patients were treated with TNF-blocker [81].

4.10.4. Autoimmune and hypersensitivity reactions

Cutaneous adverse drug reactions (CADR) may occur in patients treated with TNF-blockers. Infusion site reactions occur after subcutaneously administered ADA (24-35% vs. 16% with placebo in CLASSIC-1). Cytokine release syndrome may occur within the first hours after injection. Delayed hypersensitivity reactions might be observed typically after 3 days of drug administration. It was firstly described in adult CD patients after a long treatment ”holiday” (3-5 years) [82]. CARD15 positivity may interfere with SLE development, but coexistence of SLE and IBD is rare. However, drug (5-ASA- or TNF-blocker) induced lupus is a well-known phenomenon [83]. Biological treatment induced massive release of cellular debris leads to autoimmunity with antibody formation often seen in IBD patients [69]. On the other hand, ANA and double-stranded DNA antibody formation may occur in 53% of biologic-naive CD patients [84]. Only 0.2% of 125 CD patients developed IFX-induced lupus without major organ damage. The safety profile of ADA is similar [23]. Kappelman et al found that 737 CD patients (age: <20 years) have significantly higher prevalence of SLE (OR 41.0, 95% CI 2.3 to 719.1) compared to healthy controls [85, 86].

4.10.5. Malignancies

Since the introduction of TNF inhibitors, there has been a concern about an increase in malignancies in adults. Initial controlled trials showed, that in IFX-treated patients, regardless of the underlying disease, lymphoproliferative disorders more often developed. However, a recent meta-analysis did not demonstrate any increased risk of malignancy in this population [87]. Regarding IBD, data are inconclusive. In the meta-analysis of Williams et al, the overall risk of malignancy did not differ between patients treated with anti-TNF vs. placebo (0.77; 95% CI 0.37-1.59). In addition, there was no effect of concomitant immunosuppressant use on risk of malignancy during a one-year follow-up [88]. In the Kaiser Permanente Cancer Registry, Herrinton et al. found a standardized incidence rate ratio (SIR) of malignancies 4.4 (95% CI 3.4-5.4) in IBD patients treated with anti-TNF followed for an average of 5.8 years [89]. ADA monotherapy does not increase the incidence of cancer, while combination with other immunomodulator therapy rises the risk three-fold [90]. The TREAT registry revealed the same cancer incidence in IFX and other treatment groups in adult CD patients. We have much less information on the risk of malignancies in anti-TNF-treated children. A Swedish nationwide cohort study examined 9405 children, 3768 with CD, compared to age-, sex- and place of residence-matched healthy volunteers in a 1:10 ratio. The risk of cancer was two-fold. RR was increased in the first year after diagnosis and remained significantly higher after five years of follow-up. After the introduction of biologics, the risk of malignancies remained similar [91]. In the retrospective study of the Porto Pediatric IBD group, 18 cancers (39%) or hematologic malignancies (61%) developed between 2006-2013. Three male patients had hepatosplenic T-cell lymphoma, all of them were treated with thiopurines, any of them with biologics, only one patients suffered from CD. The solid tumors were medulloblastoma, primitive neuroectodermal tumor, pilocystic astrocytoma of the cerebellum, basal cell

carcinoma and chromophobic renal carcinoma in CD patients. Rather age then IBD seems to be the risk factor in these cases. Authors highlight, that risk of malignancies, especially of lymphomas is low in childhood, and it is unknown whether it increases with age, but extent drug-related usage can elevate the incidence of IBD associated malignancy [80]. In the prospective study of the Porto Pediatric IBD group the cancer incidence among 0-26 years aged patients did not differ significantly from the general population, fatal cancers developed at the median age of 20 years, any of the deceased patients were treated with biologics. Twenty-four from 60 malignancies occurred in patients with CD during the follow-up period (2013-2016), 4 were fatal. Twenty-two patients from 60 were exposed previously to ~~with~~ biologics. Colorectal carcinoma (CCA) occurred in four CD patients, all of them had disease confined to the colon, and disease duration to cancer was significantly longer than in patients with hematopoietic tumor (a median duration of 9.3 years versus 3.7 years). CCA was one of the most frequently reported malignancy, but only in UC patients, where all CCA cases were fatal and all patients had a concomitant diagnosis of primary sclerosing cholangitis [81].

Taken together, further research is clearly needed to clarify the risk of any infection with biologics: for pediatric patients and high-risk groups, for long-term effects, and for head-to-head comparisons between different biologics. So far, despite the short observational period, VDZ and UST are the safest agents (Table 2.).

5. Biosimilars and cost-effectiveness

Biosimilar (BS) is defined as a biological product that is highly similar to the reference product with respect to safety, purity and potency. The patent for the IFX originator (Remicade) expired in 2015 in Europe while the first BS, CT-P13 was approved by the European Medicines Agency (EMA) in 2013 and by the US Food and Drug Administration (FDA) in 2016. The access to BS and the local policies regarding the

administration of these agents vary substantially between countries. For example, Health Canada (2014) did not approve IFX BS for IBD due to insufficient amount of clinical data, molecular glycosylation differences and uncertainty resulting from small differences in antibody-dependent cell-mediated cytotoxicity [92-96]. Nevertheless, in view of the emerging data, Health Canada has now recommended BS IFX for all the indications of originator IFX by extrapolation [97]. In other countries, BS approval by regulatory agencies, a number of clinical data reports were published on BS in both adult and pediatric IBD [93, 98-106]. The NOR-SWITCH RCT trial [107] found comparable safety and efficacy in patients including IBD switching from IFX to CT-P13. A study in 692 IBD patients including 112 children did not find any age-related differences in pharmacokinetics of originator IFX, but children of different weight and age groups were not compared separately [108, 109].

Focusing only on pediatric patients in the literature, in a total of 196 pediatric CD patients treated by BS, response and remission rates were reported from 67% to 87%, respectively. In pediatric UC patients, response rates were lower and patient numbers are smaller (67) with remission rates ranging from 36% to 87%. Overall, adverse event rates were comparable to the historic data on the originator IFX.

Related to financial issue, the analysis of Jha et al. from 2015 projected one-year cumulative cost savings for usage of BS drugs in all autoimmune indications (including CD and UC) for 5 European countries (Belgium, Germany, Italy, Netherlands, UK). The estimated cumulative cost saving were substantial (with a 10% to 30% price discount) [110].

~~The~~ Studies assessing the effect of BS in economic considerations have made very conservative estimations of the economic benefits of 10-30% price discount, which is likely to underestimate the financial impact of BS, as it is suggested that price reduction could reach 60-70% [111].

6. New biological agents

6.1.Vedolizumab

In the GEMINI 1 and 2 trials published in 2013, VDZ was found to be effective in inducing and maintaining remission in adult UC and CD with remission rates of 17% and 15% at week 6, and 45% and 39% at week 52, respectively [112, 113]. More than half of CD patients had at least one type of anti-TNF therapy prior to VDZ treatment. VDZ therapy was approved in 2014 for adult CD and UC.

In a recent meta-analysis of real-world effectiveness of VDZ, remission rates in UC and CD at week 14 were 32% and 30%, respectively and at week 52 46% and 30%, respectively. Corticosteroid-free remission rates at the same time points were 26% and 25%, respectively and 42% and 31%, respectively [114]. In a retrospective multicenter European study in anti-TNF-naïve CD and UC patients treated with VDZ, clinical remission rates at week 14 were 64% and 39.5%, respectively, which is higher than reported in anti-TNF-experienced patients treated with VDZ [115].

First case series with VDZ therapy in children were published in 2016 only therefore data on VDZ in childhood CD is limited.

In a single center observational study from Philadelphia, 21 children with severe IBD (76% CD) who failed anti-TNF therapy received at least 4 infusions of VDZ (300mg at weeks 0, 2, 6 and 14) [116]. Steroid-free remission rates were 5%, 15% and 20% at weeks 6, 14 and 22, respectively. In a multi-center retrospective analysis of VDZ therapy in 52 children with IBD (58% CD, 42% UC) remission rate at week 14 was significantly higher in UC when compared to CD (76% vs 42%, respectively) [73]. Median age and median disease duration at VDZ initiation was 14.9 and 3.2 years, respectively and only 10% of children was anti-TNF naïve.

VDZ was given at weeks 0, 2 and 6 followed by approximately 8 weeks. In 75% of patients 300mg, whereas in smaller children 5-6mg/kg of VDZ was given per occasion. Higher remission rates were found at week 22 in anti-TNF naïve patients when compared to those with previous anti-TNF exposure (100% vs 45%, respectively).

The first European multi-center retrospective study on VDZ therapy in pediatric IBD was published in 2017 [117]. All of the 64 patients (36% with CD) had previous anti-TNF therapy. In 81% of children 300mg, whereas in the others 150-250mg VDZ was given. Steroid-free remission rates at week 14 and 22 were higher in UC when compared to CD (39% vs 14% and 34% vs 19%, respectively). Remission rate was not affected by concomitant immunomodulator use.

Currently VDZ can be used only as off-label in children with IBD and no pediatric dosing guidelines exist. These studies showed better outcomes with VDZ in UC and also that the onset of action was slower in CD.

Two recent single center retrospective study analyzed postoperative complications of abdominal surgery in VDZ treated pediatric patients with IBD. The one that compared postoperative complications in VDZ treated (n=13, CD=54%) and VDZ naïve (n=16, CD=12%) patients reported higher complication rate in VDZ treated group (8/13 vs 4/16, respectively) [118]. The other compared postoperative outcome in VDZ (n=13, CD=91%) and IFX (n=36, CD=72%) treated patients and found no significant differences in operative characteristics or 30-day postoperative complications [119]. None of the VDZ treated patients experienced a 30-day postoperative infectious complication.

6.2.Ustekinumab

UST was first approved to treat psoriasis in 2009 and subsequently to treat active psoriatic arthritis in 2013.

The UNITI trials, randomized, double-blind, placebo-controlled trials with UST in adults with CD, lead to the approval of UST in adult CD in 2016. UST in induction in patients with primary non-response, secondary LOR or unacceptable side effects to previous anti-TNF treatment (UNITI-1), and in patients with failure or unacceptable adverse events to conventional therapy with immunomodulators or corticosteroids (UNITI-2) was evaluated followed by the maintenance study (IM-UNITI) including patients who responded to the induction studies [12]. Response rates at week 6 with 130mg and 6mg/kg intravenous UST and placebo as induction were 34.3%, 33.7% and 21.5%, respectively in UNITI-1 and 51.7%, 55.5% and 28.7%, respectively in UNITI-2. Remission rates at week 44 with 90 mg subcutaneous UST injections every 8 or 12 weeks maintenance treatment or placebo were 53.1%, 48.8% and 35.9%, respectively. Response and remission rates with UST therapy in a real world experience from a retrospective multicenter cohort of 167 adult CD patients with refractory CD (95.2% failed anti-TNF therapy) were at 3 months 38.9% and 15%, at 6 months 60.3% and 25.2% and at 12 months 59.5% and 27.9%, respectively [120].

Data on UST treatment in childhood CD is limited with few case series reported so far. Rinawi *et al.* reported the first successful UST remission induction with 1.3 mg/kg subcutaneous injections at months 0, 1, and 3 in a 7-year-old patient with CD (failing conventional and ADA and IFX treatment) resulting in complete clinical and biochemical remission sustained with AZA for 12 months following UST induction [121]. A retrospective single center study from Seattle with UST with induction dose of 90 mg subcutaneously at weeks 0 and 4 followed by 90 mg every 8 weeks for maintenance in 4 pediatric patients with CD (age 12-17 years), all of them with prior corticosteroid, immunomodulator, IFX and ADA treatment, demonstrated clinical response in two patients who remained on UST treatment [122].

6.3 New effective biological agents currently in clinical research in CD are summarized in Table 3.

7. In utero exposure of biological agents

In female patients achieving and maintaining remission throughout pregnancy using biological agents address further questions on in utero exposure and outcome of pregnancy. A retrospective multicenter European study ("Teddy cohort") published in 2018 analyzed long-term safety of in utero exposure to anti-TNF drugs during pregnancy [123]. Incidence rate of severe infections was similar in the exposed cohort (388 children whose mother received anti-TNF agent at any time during pregnancy or during the 3 months before conception) to those in the non-exposed cohort (n=453) during 47 and 68 months of median follow-up after delivery in the exposed and the non-exposed group, respectively.

VDZ is classified as FDA pregnancy risk category B based on no fetal harm in animal studies. Complications in 25% of pregnancies and in 35% of infants (including 3 infants with congenital anomalies) in 24 pregnancies (23 live births) of female IBD patients treated with VDZ was reported in a Belgian retrospective multicenter observational study published in 2018 [124]. VDZ was stopped in the 1st and 2nd trimester in 5 and 16 patients, respectively. Fifteen woman had previous pregnancies without VDZ exposure and seven of them (47%) were complicated.

UST is classified as a pregnancy category 2 drug with no risk reported from animal studies however there are few case reports of miscarriages with maternal exposures to UST during pregnancy and only a minority of them treated for CD[125]. Healthy pregnancies, both for women and children, are also reported in several case reports with maternal UST exposure during pregnancy [126].

As there are no adequate data from the use of UST in pregnant women, therefore no final conclusion can be drawn on its safety during pregnancy. Therefore, as a precautionary measure, avoiding the use of UST or VDZ in pregnancy should be considered.

7. Expert opinion

Approximately 25% of patients with CD are diagnosed in childhood. Unfortunately, childhood-onset CD has much worse phenotype and prognosis when compared to adult-onset with a shorter window of opportunity of medical treatment of inflammatory phenotype and increased need for surgical intervention due to penetrating or stricturing disease.

T2T: Treat to Target is one of the aim of the treatment using biological agents at first where mucosal healing with clinical remission (deep remission) can be achieved.

Anti-TNF therapy is recommended for inducing remission and maintenance therapy in children with active steroid-refractory disease. In addition, anti-TNF therapy is recommended as primary induction therapy for children with active perianal fistulizing disease in combination with appropriate surgical intervention.

Patients with severe extraintestinal manifestations (e.g. pyoderma gangrenosum) should receive biologics earlier. Unfortunately, in patients with primary sclerosing cholangitits anti-TNF-agents are less effective.

For patients previously naïve to anti-TNF therapy, both IFX and ADA show comparable efficacy and adverse-events profile and could be offered to the patient according to availability, route of delivery, patient preference, cost, and local regulations. There is no evidence that IFX is more effective than ADA in CD patients with fistula.

Before starting anti-TNF therapy Tuberculosis should be excluded (chest X-ray, purified protein derivative (PPD) skin test and/or interferon gamma release assay).

Regularly scheduled (not episodic) treatment should be used to maintain remission in patients responding to induction therapy with biologics.

Primary treatment failure: primary efficacy of biologics should be assessed after the second or third dose and should be discontinued if no significant response is observed (i.e. primary treatment failure).

Although anti-TNF antibodies are potent drugs up to 40% of patients are non-responders to induction. Moreover, LOR in primary responders over time (from 6% to 46%) is another factor leading to discontinuation of that particular drug.

Combination therapy with an immunomodulator can decrease LOR and treatment intensification with dose increase and/or interval shortening can help regaining response. Therapeutic drug monitoring is the key element of decision making in children with worse prognosis and much severe phenotype and shorter window of opportunity early escalation of treatment or even starting with biological agent after diagnosis in selected patients should be considered.

There is insufficient evidence to define the risk/ benefit ratio for mono- or combination therapy in all CD children; while it seems that combination therapy for the first 6 months may be associated with a lower rate of antibodies and LOR, this benefit should be weighed against the eventually increased lymphoma risk with thiopurines on an individual basis. The use of concomitant low dose MTX is also recommended.

In patients with of partial response or LOR, measurement of serum trough level and antibodies of both IFX and ADA may facilitate decision-making whether to optimize or stop therapy. Patients with LOR infections, celiac disease, lactose intolerance, food-protein allergy and functional abdominal pain should be ruled out.

There are sufficient data to state that in children with IBD who are indicated for IFX treatment, BS (CT-P13) is a safe and efficacious alternative to the originator IFX for induction, and maintenance, of remission.

Therefore, a switch from the originator IFX to BS should be considered in children with IBD in clinical remission. Baseline trough drug levels and antibodies should be measured prior to switching, patients with persistently high antibodies should preferably switched to other drug.

To support a switch or starting BS as a first biological drug is supported by the economic benefit of BS, as it is suggested that price reduction could reach 60-70%.

Combining anti-TNF drugs (IFX or ADA) and VDZ is logical and promising therapeutic option however, further studies are needed for recommendation.

8. Article highlights box

- Childhood-onset CD has much worse phenotype and prognosis when compared to adult-onset with a shorter window of opportunity of medical treatment of inflammatory phenotype and increased need for surgical intervention due to penetrating or stricturing disease, therefore early aggressive treatment should be considered. Treat to target is one of the aim of the treatment using biological agents where mucosal healing with clinical remission (deep remission) can be achieved.
- For patients previously naïve to anti-TNF therapy, both IFX and ADA show comparable efficacy and adverse-events profile. There is no evidence that IFX is more effective than ADA in CD patients with fistula.
- Although anti-TNF antibodies are potent drugs up to 40% of patients are non-responders to induction and LOR in primary responders over time (from 6% to 46%) also leads to discontinuation of that particular drug. Combination therapy with an immunomodulator can decrease LOR and intensification of anti- TNF therapy with dose increase and/or interval shortening can help regaining response. Therapeutic drug monitoring with measurement of serum trough levels and antibodies is the key element of decision making whether to optimize or stop therapy.
- There is insufficient evidence to define the risk/ benefit ratio for mono- or combination therapy in all CD children; while it seems that combination therapy for

the first 6 months may be associated with a lower rate of antibodies and LOR, this benefit should be weighed against the eventually increased lymphoma risk with thiopurines on an individual basis.

- Biosimilar (BS) (CT-P13) is a safe and efficacious alternative to the originator IFX for induction, and maintenance, of remission in children with IBD who are indicated for IFX treatment. To support a switch from the originator IFX to BS or starting BS as a first biological drug is supported by the economic benefit of BS, as it is suggested that price reduction could reach 60-70%.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Benchimol, E.I., et al., *Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends.* Inflamm Bowel Dis, 2011. **17**(1): p. 423-39.
2. Ruel, J., et al., *IBD across the age spectrum: is it the same disease?* Nat Rev Gastroenterol Hepatol, 2014. **11**(2): p. 88-98.
3. Ruemmele, F.M., et al., *Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease.* J Crohns Colitis, 2014. **8**(10): p. 1179-207.

   * This article provides consensus-based recommendations on medical treatment of pediatric Crohn's disease

4. Lobo, E.D., R.J. Hansen, and J.P. Balthasar, *Antibody pharmacokinetics and pharmacodynamics.* J Pharm Sci, 2004. **93**(11): p. 2645-68.
5. Wyant, T., E. Fedyk, and B. Abhyankar, *An Overview of the Mechanism of Action of the Monoclonal Antibody Vedolizumab.* J Crohns Colitis, 2016. **10**(12): p. 1437-1444.
6. Benson, J.M., et al., *Discovery and mechanism of ustekinumab: a human monoclonal antibody targeting interleukin-12 and interleukin-23 for treatment of immune-mediated disorders.* MAbs, 2011. **3**(6): p. 535-45.
7. Vande Casteele, N. and A. Gils, *Pharmacokinetics of anti-TNF monoclonal antibodies in inflammatory bowel disease: Adding value to current practice.* J Clin Pharmacol, 2015. **55 Suppl 3**: p. S39-50.
8. Kaymakcalan, Z., et al., *Comparisons of affinities, avidities, and complement activation of adalimumab, infliximab, and etanercept in binding to soluble and membrane tumor necrosis factor.* Clin Immunol, 2009. **131**(2): p. 308-16.
9. Levin, A.D., et al., *Autophagy Contributes to the Induction of Anti-TNF Induced Macrophages.* Journal of Crohn's & colitis, 2016. **10**(3): p. 323-329.
10. Zundler, S. and M.F. Neurath, *Novel Insights into the Mechanisms of Gut Homing and Antiadhesion Therapies in Inflammatory Bowel Diseases.* Inflamm Bowel Dis, 2017. **23**(4): p. 617-627.

    *The paper extensively reviews the more advanced pharamacological aspect of specific gut homing of the biologicals. This aspect is central in the current frontiers of drug discovery and desing in the biological therapies of IBD

11. Simon, E.G., et al., *Ustekinumab: a novel therapeutic option in Crohn's disease.* Expert Opinion on Biological Therapy, 2016. **16**(8): p. 1065-1074.
12. Feagan, B.G., et al., *Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease.* N Engl J Med, 2016. **375**(20): p. 1946-1960.
13. Jaramillo, C.A.C., et al., *Toward in vitro-to-in vivo translation of monoclonal antibody pharmacokinetics: Application of a neonatal Fc receptor-mediated transcytosis assay to understand the interplaying clearance mechanisms.* MAbs, 2017. **9**(5): p. 781-791.
14. Hemperly, A. and N. Vande Casteele, *Clinical Pharmacokinetics and Pharmacodynamics of Infliximab in the Treatment of Inflammatory Bowel Disease.* Clin Pharmacokinet, 2018.
15. Rosario, M., et al., *A Review of the Clinical Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Vedolizumab.* Clin Pharmacokinet, 2017. **56**(11): p. 1287-1301.

16. Dotan, I., et al., *Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study.* Inflamm Bowel Dis, 2014. **20**(12): p. 2247-59.
17. Sharma, S., et al., *Pharmacokinetics and exposure-efficacy relationship of adalimumab in pediatric patients with moderate to severe Crohn's disease: results from a randomized, multicenter, phase-3 study.* Inflamm Bowel Dis, 2015. **21**(4): p. 783-92.
18. Zhu, Y., et al., *Population pharmacokinetic modeling of ustekinumab, a human monoclonal antibody targeting IL-12/23p40, in patients with moderate to severe plaque psoriasis.* J Clin Pharmacol, 2009. **49**(2): p. 162-75.
19. Hanauer, S.B., et al., *Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial.* The Lancet, 2002. **359**(9317): p. 1541-1549.
20. Rutgeerts, P., et al., *Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease.* Gastroenterology, 2004. **126**(2): p. 402-413.
21. Hyams, J., et al., *Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children.* Gastroenterology, 2007. **132**(3): p. 863-73.
22. Hanauer, S.B., et al., *Human Anti-Tumor Necrosis Factor Monoclonal Antibody (Adalimumab) in Crohn's Disease: the CLASSIC-I Trial.* Gastroenterology, 2006. **130**(2): p. 323-333.
23. Sandborn, W.J., et al., *Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial.* Gut, 2007. **56**(9): p. 1232-9.
24. Hyams, J.S., et al., *Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children.* Gastroenterology, 2012. **143**(2): p. 365-74 e2.
25. Cozijnsen, M., et al., *Adalimumab therapy in children with Crohn disease previously treated with infliximab.* J Pediatr Gastroenterol Nutr, 2015. **60**(2): p. 205-10.
26. Kierkus, J., et al., *The impact of infliximab induction therapy on mucosal healing and clinical remission in Polish pediatric patients with moderate-to-severe Crohn's disease.* Eur J Gastroenterol Hepatol, 2012. **24**(5): p. 495-500.
27. Carla-Moreau, A., et al., *Prevention and treatment of postoperative Crohn's disease recurrence with anti-TNF therapy: a meta-analysis of controlled trials.* Dig Liver Dis, 2015. **47**(3): p. 191-6.
28. Nuti, F., et al., *Prospective Evaluation of the Achievement of Mucosal Healing with Anti-TNF-alpha Therapy in a Paediatric Crohn's Disease Cohort.* J Crohns Colitis, 2016. **10**(1): p. 5-12.
29. Nobile, S., et al., *Mucosal healing in pediatric Crohn's disease after anti-TNF therapy: a long-term experience at a single center.* European Journal of Gastroenterology & Hepatology, 2014. **26**(4): p. 458-465.
30. Walters, T.D., et al., *Increased effectiveness of early therapy with anti-tumor necrosis factor-alpha vs an immunomodulator in children with Crohn's disease.* Gastroenterology, 2014. **146**(2): p. 383-91.
31. Kang, B., et al., *Mucosal Healing in Paediatric Patients with Moderate-to-Severe Luminal Crohn's Disease Under Combined Immunosuppression: Escalation versus Early Treatment.* Journal of Crohn's and Colitis, 2016. **10**(11): p. 1279-1286.
32. Kugathasan, S., et al., *Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study.* The Lancet, 2017. **389**(10080): p. 1710-1718.
33. Assa, A., et al., *Long-term outcome of tumor necrosis factor alpha antagonist's treatment in pediatric Crohn's disease.* J Crohns Colitis, 2013. **7**(5): p. 369-76.
34. Nuti, F., et al., *Biological Therapy in a Pediatric Crohn Disease Population at a Referral Center.* Journal of Pediatric Gastroenterology and Nutrition, 2014. **58**(5): p. 582-587.
35. De Bie, C.I., et al., *The duration of effect of infliximab maintenance treatment in paediatric Crohn's disease is limited.* Alimentary Pharmacology & Therapeutics, 2011. **33**(2): p. 243-250.
36. Grossi, V., et al., *Concomitant Use of Immunomodulators Affects the Durability of Infliximab Therapy in Children With Crohn's Disease.* Clin Gastroenterol Hepatol, 2015. **13**(10): p. 1748-56.

37. deBruyn, J.C., et al., *Long-term Outcomes of Infliximab Use for Pediatric Crohn Disease: A Canadian Multicenter Clinical Practice Experience.* J Pediatr Gastroenterol Nutr, 2018. **66**(2): p. 268-273.
38. Faubion, W.A., et al., *Long-term Efficacy and Safety of Adalimumab in Pediatric Patients with Crohn's Disease.* Inflamm Bowel Dis, 2017. **23**(3): p. 453-460.

39. Singh, S., et al., *Comparison of infliximab with adalimumab in 827 biologic-naive patients with Crohn's disease: a population-based Danish cohort study.* Aliment Pharmacol Ther, 2018. **47**(5): p. 596-604.

**In this nationwide propensity score matched cohort of truly biologic-naïve adults with CD no significant difference in effectiveness and safety of adalimumab and infliximab could be found.

40. Olivera, P., et al., *Treatment Persistence for Infliximab Versus Adalimumab in Crohn's Disease: A 14-Year Single-Center Experience.* Inflamm Bowel Dis, 2017. **23**(6): p. 976-985.
41. Colombel , J.F., et al., *Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease.* New England Journal of Medicine, 2010. **362**(15): p. 1383-1395.
42. Feagan, B.G., et al., *Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease.* Gastroenterology, 2014. **146**(3): p. 681-688 e1.
43. Church, P.C., et al., *Infliximab Maintains Durable Response and Facilitates Catch-up Growth in Luminal Pediatric Crohn's Disease.* Inflammatory Bowel Diseases, 2014. **20**(7): p. 1177-1186.
44. Ungar, B., et al., *Addition of an immunomodulator can reverse antibody formation and loss of response in patients treated with adalimumab.* Aliment Pharmacol Ther, 2017. **45**(2): p. 276-282.
45. Strik, A.S., et al., *Suppression of anti-drug antibodies to infliximab or adalimumab with the addition of an immunomodulator in patients with inflammatory bowel disease.* Aliment Pharmacol Ther, 2017. **45**(8): p. 1128-1134.
46. Ding, N.S., A. Hart, and P. De Cruz, *Systematic review: predicting and optimising response to anti-TNF therapy in Crohn's disease - algorithm for practical management.* Aliment Pharmacol Ther, 2016. **43**(1): p. 30-51.
47. Ben-Horin, S. and Y. Chowers, *Review article: loss of response to anti-TNF treatments in Crohn's disease.* Aliment Pharmacol Ther, 2011. **33**(9): p. 987-95.
48. Vande Casteele, N., et al., *Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease.* Gastroenterology, 2015. **148**(7): p. 1320-9 e3.
49. Kansen, H.M., et al., *Less Anti-infliximab Antibody Formation in Paediatric Crohn Patients on Concomitant Immunomodulators.* J Pediatr Gastroenterol Nutr, 2017. **65**(4): p. 425-429.
50. Dupont-Lucas, C., et al., *Identifying Patients at High Risk of Loss of Response to Infliximab Maintenance Therapy in Paediatric Crohn's Disease.* J Crohns Colitis, 2016. **10**(7): p. 795-804.
51. van Hoeve, K., et al., *Higher Infliximab Trough Levels Are Associated With Better Outcome in Paediatric Patients With Inflammatory Bowel Disease.* J Crohns Colitis, 2018. **12**(11): p. 1316-1325.

** This retrospective study in pediatric patients with CD showed that proactive therapeutic drug monitoring with dose adjustment resulted in higher endoscopic and clinical remission rates associated with higher IFX trough levels

52. Louis, E., et al., *Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped.* Gastroenterology, 2012. **142**(1): p. 63-70 e5; quiz e31.

53. Van Assche, G., et al., *Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial.* Gastroenterology, 2008. **134**(7): p. 1861-8.
54. Cseh, Á., et al., *Long-term follow-up in children with Crohn's disease with infliximab therapy: the PIT-STOP multicenter study.* Journal of Pediatric Gastroenterology and Nutrition, 2017. **64**(Supplement 1): p. 464.
55. Molnár, T., et al., *Predictors of relapse in patients with Crohn's disease in remission after 1 year of biological therapy.* Alimentary Pharmacology & Therapeutics, 2013. **37**(2): p. 225-233.
56. Pigneur, B., et al., *Natural history of Crohn's disease: comparison between childhood- and adult-onset disease.* Inflamm Bowel Dis, 2010. **16**(6): p. 953-61.
57. Eberhardson, M., et al., *Anti-TNF treatment in Crohn's disease and risk of bowel resection-a population based cohort study.* Aliment Pharmacol Ther, 2017. **46**(6): p. 589-598.
58. Assa, A., et al., *Anti-TNFalpha Treatment After Surgical Resection for Crohn's Disease Is Effective Despite Previous Pharmacodynamic Failure.* Inflamm Bowel Dis, 2017. **23**(5): p. 791-797.
59. Singh, S., et al., *Comparative efficacy of pharmacologic interventions in preventing relapse of Crohn's disease after surgery: a systematic review and network meta-analysis.* Gastroenterology, 2015. **148**(1): p. 64-76.e2; quiz e14.
60. Splawski, J.B., et al., *NASPGHAN Clinical Report on Postoperative Recurrence in Pediatric Crohn Disease.* J Pediatr Gastroenterol Nutr, 2017. **65**(4): p. 475-486.
61. Diederen, K., et al., *Complications and Disease Recurrence After Primary Ileocecal Resection in Pediatric Crohn's Disease: A Multicenter Cohort Analysis.* Inflamm Bowel Dis, 2017. **23**(2): p. 272-282.
62. Sands , B.E., et al., *Infliximab Maintenance Therapy for Fistulizing Crohn's Disease.* New England Journal of Medicine, 2004. **350**(9): p. 876-885.
63. Colombel, J.F., et al., *Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial.* Gastroenterology, 2007. **132**(1): p. 52-65.
64. Crandall, W., et al., *Infliximab Therapy in Children With Concurrent Perianal Crohn Disease: Observations From REACH.* Journal of Pediatric Gastroenterology and Nutrition, 2009. **49**(2): p. 183-190.
65. Dupont-Lucas, C., et al., *Predictors of response to infliximab in paediatric perianal Crohn's disease.* Alimentary Pharmacology & Therapeutics, 2014. **40**(8): p. 917-929.
66. Assa, A., et al., *Perianal Pediatric Crohn Disease Is Associated With a Distinct Phenotype and Greater Inflammatory Burden.* J Pediatr Gastroenterol Nutr, 2017. **65**(3): p. 293-298.
67. Amil-Dias, J., et al., *Surgical Management of Crohn Disease in Children: Guidelines From the Paediatric IBD Porto Group of ESPGHAN.* Journal of Pediatric Gastroenterology and Nutrition, 2017. **64**(5): p. 818-835.

*This article provides evidence-based guidance on surgical management of pediatric CD

68. Ji, C.C. and S. Takano, *Clinical efficacy of adalimumab versus infliximab and the factors associated with recurrence or aggravation during treatment of anal fistulas in Crohn's disease.* Intest Res, 2017. **15**(2): p. 182-186.
69. D'Haens, G., *Risks and benefits of biologic therapy for inflammatory bowel diseases.* Gut, 2007. **56**(5): p. 725-732.
70. Freling, E., et al., *Cumulative incidence of, risk factors for, and outcome of dermatological complications of anti-TNF therapy in inflammatory bowel disease: a 14-year experience.* Am J Gastroenterol, 2015. **110**(8): p. 1186-96.
71. Andrade, P., et al., *Anti-Tumor Necrosis Factor-alpha-Induced Dermatological Complications in a Large Cohort of Inflammatory Bowel Disease Patients.* Dig Dis Sci, 2018. **63**(3): p. 746-754.

72. Malkonen, T., et al., *Skin reactions during anti-TNFalpha therapy for pediatric inflammatory bowel disease: a 2-year prospective study.* Inflamm Bowel Dis, 2014. **20**(8): p. 1309-15.
73. Singh, N., et al., *Multi-Center Experience of Vedolizumab Effectiveness in Pediatric Inflammatory Bowel Disease.* Inflamm Bowel Dis, 2016. **22**(9): p. 2121-6.
74. Gupta, G., J.M. Gelfand, and J.D. Lewis, *Increased risk for demyelinating diseases in patients with inflammatory bowel disease.* Gastroenterology, 2005. **129**(3): p. 819-26.
75. Tristano, A.G., *Neurological adverse events associated with anti-tumor necrosis factor alpha treatment.* J Neurol, 2010. **257**(9): p. 1421-31.
76. Ramos-Casals, M., et al., *Autoimmune diseases induced by biological agents: a double-edged sword?* Autoimmun Rev, 2010. **9**(3): p. 188-93.
77. Ford, A.C. and L. Peyrin-Biroulet, *Opportunistic infections with anti-tumor necrosis factor-alpha therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials.* Am J Gastroenterol, 2013. **108**(8): p. 1268-76.
78. Peyrin-Biroulet, L., et al., *Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials.* Clin Gastroenterol Hepatol, 2008. **6**(6): p. 644-53.
79. Stoll, M.L., et al., *Risk of tuberculosis among Alabama children and adolescents treated with tumor necrosis factor inhibitors: a retrospective study.* Pediatr Rheumatol Online J, 2017. **15**(1): p. 79.
80. de Ridder, L., et al., *Malignancy and mortality in pediatric patients with inflammatory bowel disease: a multinational study from the porto pediatric IBD group.* Inflamm Bowel Dis, 2014. **20**(2): p. 291-300.
81. Joosse, M.E., et al., *Malignancy and mortality in paediatric-onset inflammatory bowel disease: a 3-year prospective, multinational study from the paediatric IBD Porto group of ESPGHAN.* Aliment Pharmacol Ther, 2018. **48**(5): p. 523-537.

*First multinational prospective study by Porto Pediatric IBD Group, which found no significant difference in cancer incidence among pediatric IBD patients compared to general population.

82. Hanauer, S., et al., *Delayed hypersensitivity to infliximab [Remicade] re-infusion after a 2–4 year interval without treatment.* Gastroenterology, 1999. **116**(A731).
83. Katsanos, K.H., P.V. Voulgari, and E.V. Tsianos, *Inflammatory bowel disease and lupus: a systematic review of the literature.* J Crohns Colitis, 2012. **6**(7): p. 735-42.
84. Tsuchiya, M., et al., *Radiographic and endoscopic features of colonic ulcers in systemic lupus erythematosus.* Am J Gastroenterol, 1975. **64**(4): p. 277-85.
85. Vermeire, S. and P. Rutgeerts, *Antibody responses in Crohn’s disease.* Gastroenterology, 2004. **126**(2): p. 601-604.
86. Kappelman, M.D., et al., *Association of paediatric inflammatory bowel disease with other immune-mediated diseases.* Arch Dis Child, 2011. **96**(11): p. 1042-6.
87. Lopez-Olivo, M.A., et al., *Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis.* Jama, 2012. **308**(9): p. 898-908.
88. Williams, C.J., L. Peyrin-Biroulet, and A.C. Ford, *Systematic review with meta-analysis: malignancies with anti-tumour necrosis factor-alpha therapy in inflammatory bowel disease.* Aliment Pharmacol Ther, 2014. **39**(5): p. 447-58.
89. Herrinton, L.J., et al., *Role of thiopurine and anti-TNF therapy in lymphoma in inflammatory bowel disease.* Am J Gastroenterol, 2011. **106**(12): p. 2146-53.

90. Osterman, M.T., et al., *Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease.* Gastroenterology, 2014. **146**(4): p. 941-9.
91. Olen, O., et al., *Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964-2014.* Bmj, 2017. **358**: p. j3951.
92. *Summary Basis of Decision (SBD): Remsima. Available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-ed/sbd_smd_2014_remsima_160195-eng.php.* Health Canada, 2015.
93. Buer, L., et al., *Does the Introduction of Biosimilars Change Our Understanding about Treatment Modalities for Inflammatory Bowel Disease?* Dig Dis, 2017. **35**(1-2): p. 74-82.
94. Feagan, B.G., et al., *The challenge of indication extrapolation for infliximab biosimilars.* Biologicals, 2014. **42**(4): p. 177-83.
95. Gomollon, F., *Biosimilars: are they bioequivalent?* Dig Dis, 2014. **32 Suppl 1**: p. 82-7.
96. Zheng, M.K., D.Q. Shih, and G.C. Chen, *Insights on the use of biosimilars in the treatment of inflammatory bowel disease.* World J Gastroenterol, 2017. **23**(11): p. 1932-1943.
97. *Canadian Agency for Drugs and Technologies in Health. Switching from Innovator to Biosimilar (Subsequent Entry) Infliximab: An Updated Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Ottawa (ON)*. 2017.
98. Farkas, K., et al., *Efficacy of the new infliximab biosimilar CT-P13 induction therapy in Crohn's disease and ulcerative colitis - experiences from a single center.* Expert Opin Biol Ther, 2015. **15**(9): p. 1257-62.
99. Gecse, K.B., et al., *Efficacy and Safety of the Biosimilar Infliximab CT-P13 Treatment in Inflammatory Bowel Diseases: A Prospective, Multicentre, Nationwide Cohort.* J Crohns Colitis, 2016. **10**(2): p. 133-40.
100. Ha, C.Y. and A. Kornbluth, *A Critical Review of Biosimilars in IBD: The Confluence of Biologic Drug Development, Regulatory Requirements, Clinical Outcomes, and Big Business.* Inflamm Bowel Dis, 2016. **22**(10): p. 2513-26.
101. Jahnsen, J., et al., *Biosimilar infliximab (CT-P13) in the treatment of inflammatory bowel disease: A Norwegian observational study.* Expert Rev Gastroenterol Hepatol, 2015. **9 Suppl 1**: p. 45-52.
102. Jung, Y.S., et al., *Efficacy and safety of CT-P13, a biosimilar of infliximab, in patients with inflammatory bowel disease: A retrospective multicenter study.* J Gastroenterol Hepatol, 2015. **30**(12): p. 1705-12.
103. Keil, R., et al., *Clinical monitoring: infliximab biosimilar CT-P13 in the treatment of Crohn's disease and ulcerative colitis.* Scand J Gastroenterol, 2016. **51**(9): p. 1062-8.
104. Park, D.I., *Current status of biosimilars in the treatment of inflammatory bowel diseases.* Intest Res, 2016. **14**(1): p. 15-20.
105. Sieczkowska, J., et al., *Switching Between Infliximab Originator and Biosimilar in Paediatric Patients with Inflammatory Bowel Disease. Preliminary Observations.* J Crohns Colitis, 2016. **10**(2): p. 127-32.
106. Sieczkowska, J., et al., *Experience with biosimilar infliximab (CT-P13) in paediatric patients with inflammatory bowel diseases.* Therap Adv Gastroenterol, 2016. **9**(5): p. 729-35.
107. Jorgensen, K.K., et al., *Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial.* Lancet, 2017. **389**(10086): p. 2304-2316.
108. Fasanmade, A.A., et al., *Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials.* Clin Ther, 2011. **33**(7): p. 946-64.
109. Jongsma, M.M.E., A. Vulto, and L. de Ridder, *The use of biosimilars in paediatric inflammatory bowel disease.* Curr Opin Pediatr, 2017. **29**(5): p. 560-565.
110. Jha, A., et al., *The Budget Impact of Biosimilar Infliximab (Remsima(R)) for the Treatment of Autoimmune Diseases in Five European Countries.* Adv Ther, 2015. **32**(8): p. 742-56.

111. Kanters, T.A., et al., *Adoption of Biosimilar Infliximab for Rheumatoid Arthritis, Ankylosing Spondylitis, and Inflammatory Bowel Diseases in the EU5: A Budget Impact Analysis Using a Delphi Panel.* Front Pharmacol, 2017. **8**: p. 322.
112. Feagan, B.G., et al., *Vedolizumab as induction and maintenance therapy for ulcerative colitis.* N Engl J Med, 2013. **369**(8): p. 699-710.
113. Sandborn, W.J., et al., *Vedolizumab as induction and maintenance therapy for Crohn's disease.* N Engl J Med, 2013. **369**(8): p. 711-21.
114. Schreiber, S., et al., *Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease.* J Gastroenterol, 2018. **53**(9): p. 1048-1064.
115. Kopylov, U., et al., *Effectiveness and Safety of Vedolizumab in Anti-TNF-Naïve Patients With Inflammatory Bowel Disease—A Multicenter Retrospective European Study.* Inflammatory Bowel Diseases, 2018: p. izy155-izy155.
116. Conrad, M.A., et al., *Vedolizumab Therapy in Severe Pediatric Inflammatory Bowel Disease.* Inflamm Bowel Dis, 2016. **22**(10): p. 2425-31.
117. Ledder, O., et al., *Vedolizumab in Paediatric Inflammatory Bowel Disease: A Retrospective Multi-Centre Experience From the Paediatric IBD Porto Group of ESPGHAN.* Journal of Crohn's and Colitis, 2017. **11**(10): p. 1230-1237.
118. Zimmerman, L.A., et al., *Postoperative complications of pediatric patients with inflammatory bowel disease treated with vedolizumab.* J Pediatr Surg, 2018. **53**(7): p. 1330-1333.
119. Lightner, A.L., et al., *Postoperative outcomes in vedolizumab-treated pediatric patients undergoing abdominal operations for inflammatory bowel disease.* J Pediatr Surg, 2018. **53**(9): p. 1706-1709.
120. Ma, C., et al., *Clinical, endoscopic and radiographic outcomes with ustekinumab in medically-refractory Crohn's disease: real world experience from a multicentre cohort.* Aliment Pharmacol Ther, 2017. **45**(9): p. 1232-1243.
121. Rinawi, F., et al., *Ustekinumab for Resistant Pediatric Crohn Disease.* J Pediatr Gastroenterol Nutr, 2016. **62**(4): p. e34-5.
122. Bishop, C., et al., *Ustekinumab in Pediatric Crohn Disease Patients.* J Pediatr Gastroenterol Nutr, 2016. **63**(3): p. 348-51.
123. Chaparro, M., et al., *Long-Term Safety of In Utero Exposure to Anti-TNFalpha Drugs for the Treatment of Inflammatory Bowel Disease: Results from the Multicenter European TEDDY Study.* Am J Gastroenterol, 2018. **113**(3): p. 396-403.
124. Moens, A., et al., *Outcome of Pregnancies in Female Patients With Inflammatory Bowel Diseases Treated With Vedolizumab.* J Crohns Colitis, 2018.
125. Venturin, C., et al., *Fetal death in utero and miscarriage in a patient with Crohn's disease under therapy with ustekinumab: case-report and review of the literature.* BMC Gastroenterology, 2017. **17**(1).
126. Galluzzo, M., et al., *Psoriasis in pregnancy: case series and literature review of data concerning exposure during pregnancy to ustekinumab.* Journal of Dermatological Treatment, 2018: p. 1-5.
127. Selinger, C., et al., *OTU-003 Etrolizumab as induction therapy in moderate to severe crohn's disease: results from bergamot cohort 1.* Gut, 2018. **67**(Suppl 1): p. A53-A53.
128. Feagan, B.G., et al., *Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study.* Lancet, 2017. **389**(10080): p. 1699-1709.
129. Feagan, B.G., et al., *Efficacy and Safety of Open-Label Maintenance Therapy with Subcutaneous Risankizumab in Patients with Moderateto-Severe Crohn's Disease.* Gastroenterology, 2017. **152**(5): p. S1310.
130. Sandborn, W.J., et al., *Safety and Efficacy of ABT-494 (Upadacitinib), an Oral Jak1 Inhibitor, as Induction Therapy in Patients with Crohn's Disease: Results from Celest.* Gastroenterology, 2017. **152**(5): p. S1308-S1309.

131. Vermeire, S., et al., *Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial.* Lancet, 2017. **389**(10066): p. 266-275.
132. Feagan, B. and W. Sandborn *Endoscopic and Clinical Efficacy Demonstrated With Oral Ozanimod in Moderately to Severely Active Crohn's Disease. Program No. P1272. World Congress of Gastroenterology at ACG2017 Meeting Abstracts.* United European Gastroenterology Journal, 2017. **5**(supplement 1).
133. Danese, S., et al., *Randomised trial and open-label extension study of an anti-interleukin-6 antibody in Crohn's disease (ANDANTE I and II).* Gut, 2017.

Table 1.: Indicators for complicated disease course in pediatric CD

Indicators for complicated disease course in pediatric CD:	
At presentation:	
	Extensive (pan-enteric) disease
	Deep colonic ulcerations on endoscopy
	Stricturing and penetrating disease
	Severe perianal disease
	Significant growth delay
	Severe osteoporosis
	High serum C-reactive protein (CRP)
	Increased serologic reactivity to microbial antigens
Early use of corticosteroids (more likely indicator for severe disease)	
Severe disease despite adequate induction therapy	

Table 2. Side effects of infliximab, adalimumab and vedozilumab

	Infliximab	**Adalimumab**	**Vedolizumab**
Serious infections	+	+	-
Granulomatous infection	+	+	-
Demyelinating	+	+	-
Non-Hodgkin's lymphoma	+	+	-

Table 3.

New effective biological agents in Crohn's disease

Agent	Target	Formulation	Administration	Status	
				Adult [A]	Pediatric
etrolizumab	β7-integrin	Humanized mAb	s.c.	Phase III (BERGAMOT) [127]	no studies
risankizumab	p19 subunit of IL-23	Humanized mAb	i.v./s.c.	Phase II [128, 129]	no studies
upadacitinib	JAK1	small molecule	oral	Phase II (CELEST) [130]	no studies
filgotinib	JAK1	small molecule	oral	Phase II (FITZROY) [131]	no studies
ozanimod	S1P1R and S1P5R	small molecule	oral	Phase II (STEPSTONE) [132]	no studies
PF-04236921	IL-6	Fully human mAb	s.c.	Phase II (ANDANTE) [133]	no studies

abbreviations:

s.c. – subcutaneous injection

i.v. - intravenous

mAb – monoclonal antibody

IL – interleukin

JAK1 – Janus Kinase 1

S1P1R - sphingosine-1-phosphate 1 receptor

S1P5R - sphingosine-1-phosphate 5 receptor

[A] Highest level of completed clinical studies, obtained from www.clinicaltrials.gov, accessed on 20th November 2018.